Les recommandations du PRAC
La FAI2R vous informe

Christophe Richez,

Bordeaux

Conflits d’intérêts

- Intérêts financiers : Aucun
- Liens durables ou permanents : Aucun
- Financements de recherche : Biogen, Lilly, Glenmark et Nordic Pharma
- Interventions ponctuelles et expertise : Abbvie, Amgen, Astra Zeneca, Biogen, BMS, Glenmark, GSK, Lilly, MSD, Mylan et Pfizer
- Intérêts indirects : Aucun

Pourquoi ce PRAC ?

- ORAL Surveillance
- B023

The NEW ENGLAND JOURNAL of MEDICINE

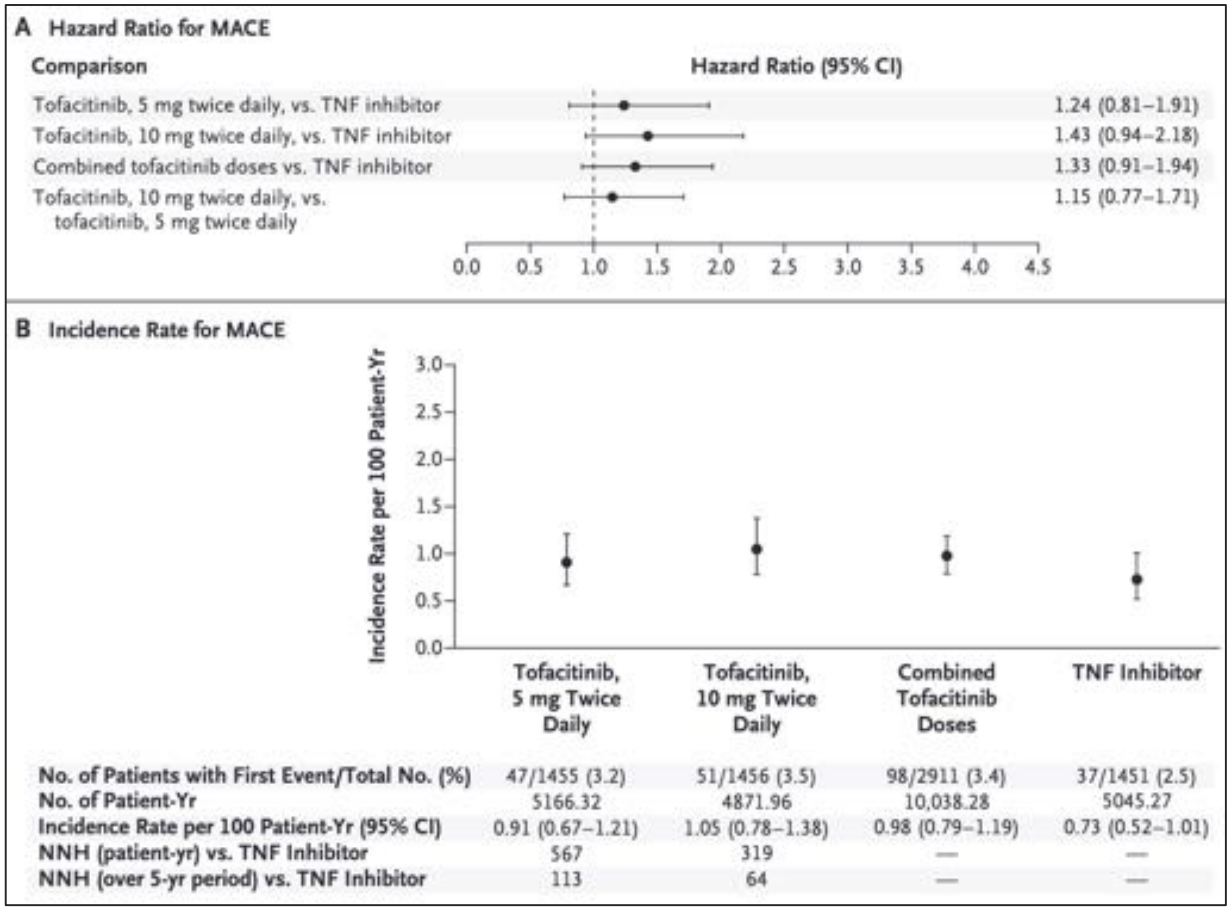
ORIGINAL ARTICLE

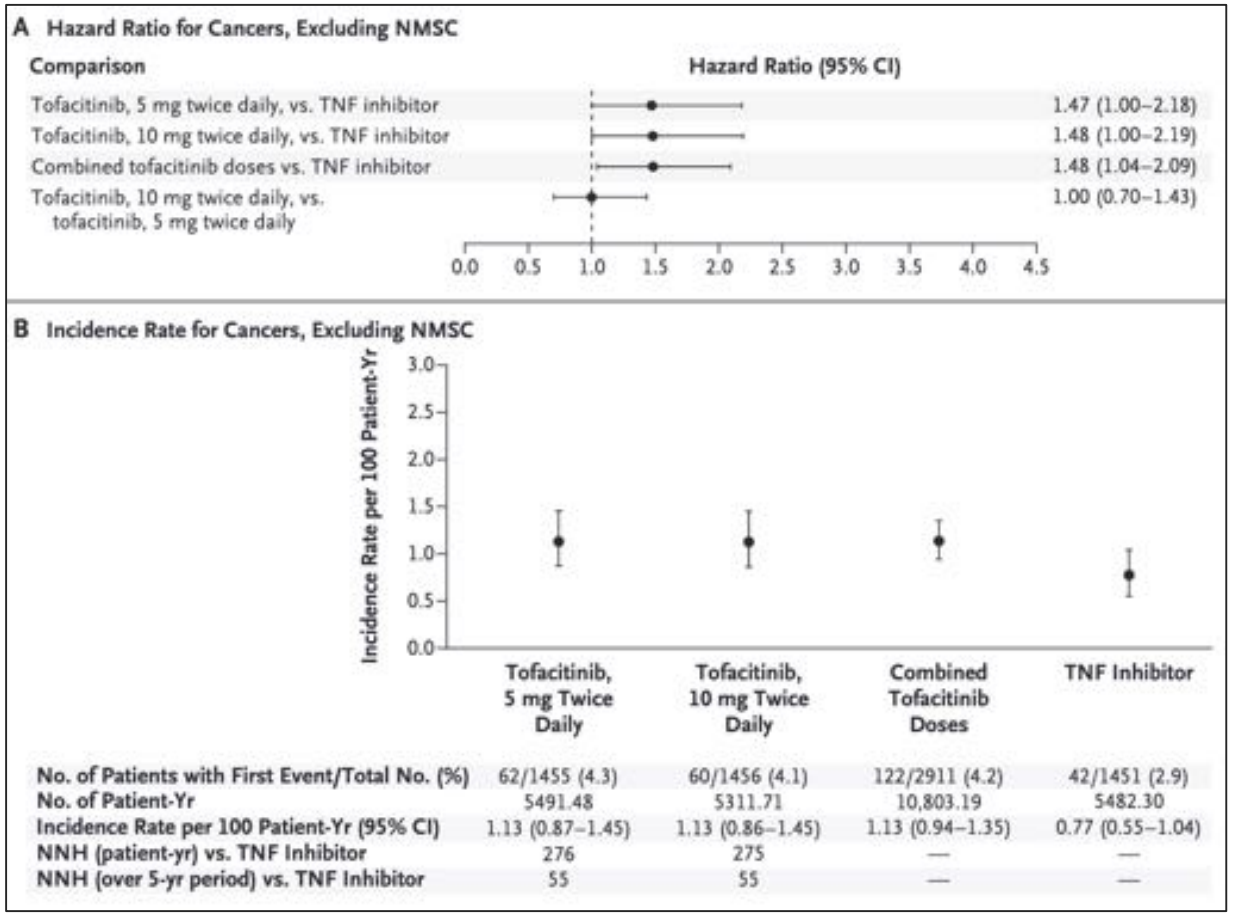
Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

ORAL surveillance : MACE et risque néoplasique





Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

Rheumatol Ther
https://doi.org/10.1007/s40744-022-00505-1

ORIGINAL RESEARCH

Evaluation of VTE, MACE, and Serious Infections Among Patients with RA Treated with Baricitinib Compared to TNFi: A Multi-Database Study of Patients in Routine Care Using Disease Registries and Claims Databases

- Patients atteints de PR provenant de 14 bases de données différentes : US (n = 9) ; Europe (n = 3) ; Japon (n = 2)
- Appariement par score de propension (1:1) pour essayer d'éliminer les facteurs de confusion potentiels.
- Méta-analyse des rapports de taux d'incidence (IRR) et des différences de taux d'incidence (IRD) (régression de Poisson modifiée et analyse de Cochran-Mantel-Haenszel)

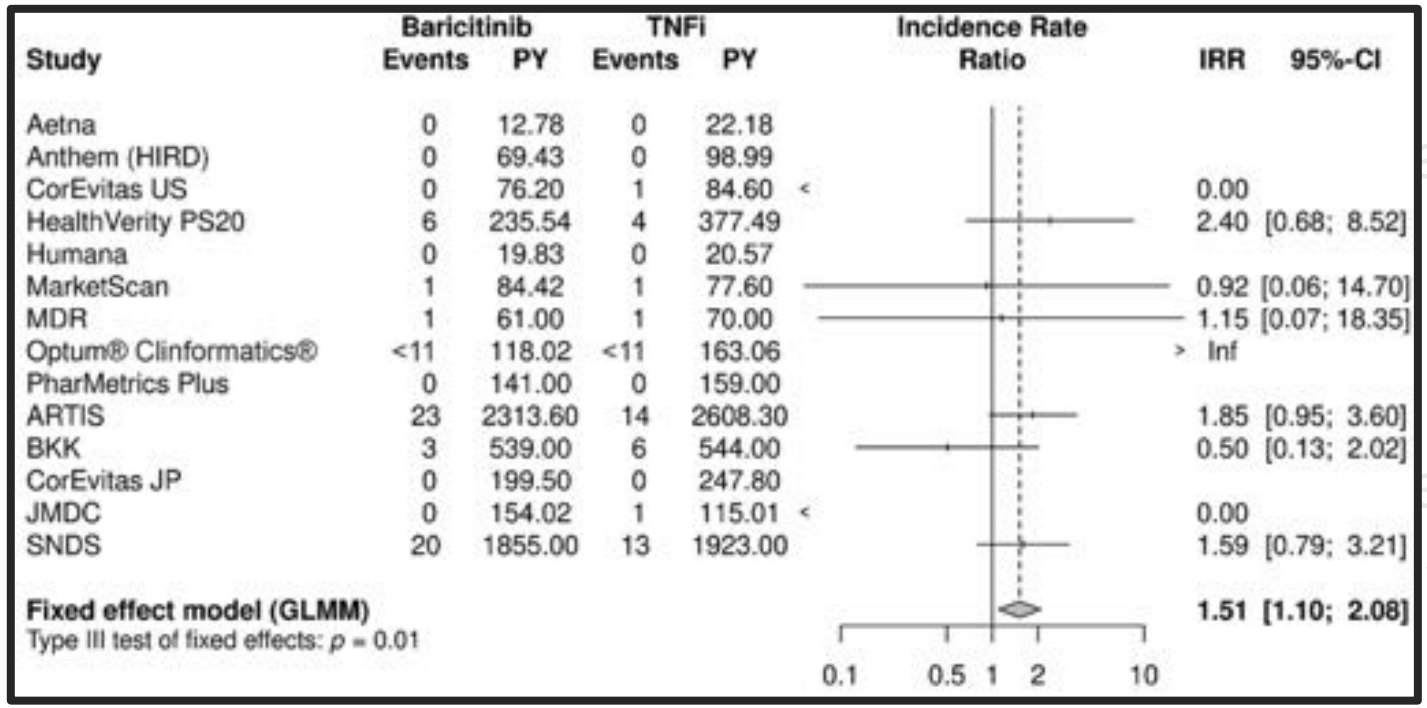
Salinas CA, et al. Rheumatol Ther. 2022 Nov 13:1–23

Rheumatol Ther
https://doi.org/10.1007/s40744-022-00505-1

ORIGINAL RESEARCH

Evaluation of VTE, MACE, and Serious Infections Among Patients with RA Treated with Baricitinib Compared to TNFi: A Multi-Database Study of Patients in Routine Care Using Disease Registries and Claims Databases

VTE



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Salinas CA, et al. Rheumatol Ther. 2022 Nov 13:1–23

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ORIGINAL RESEARCH

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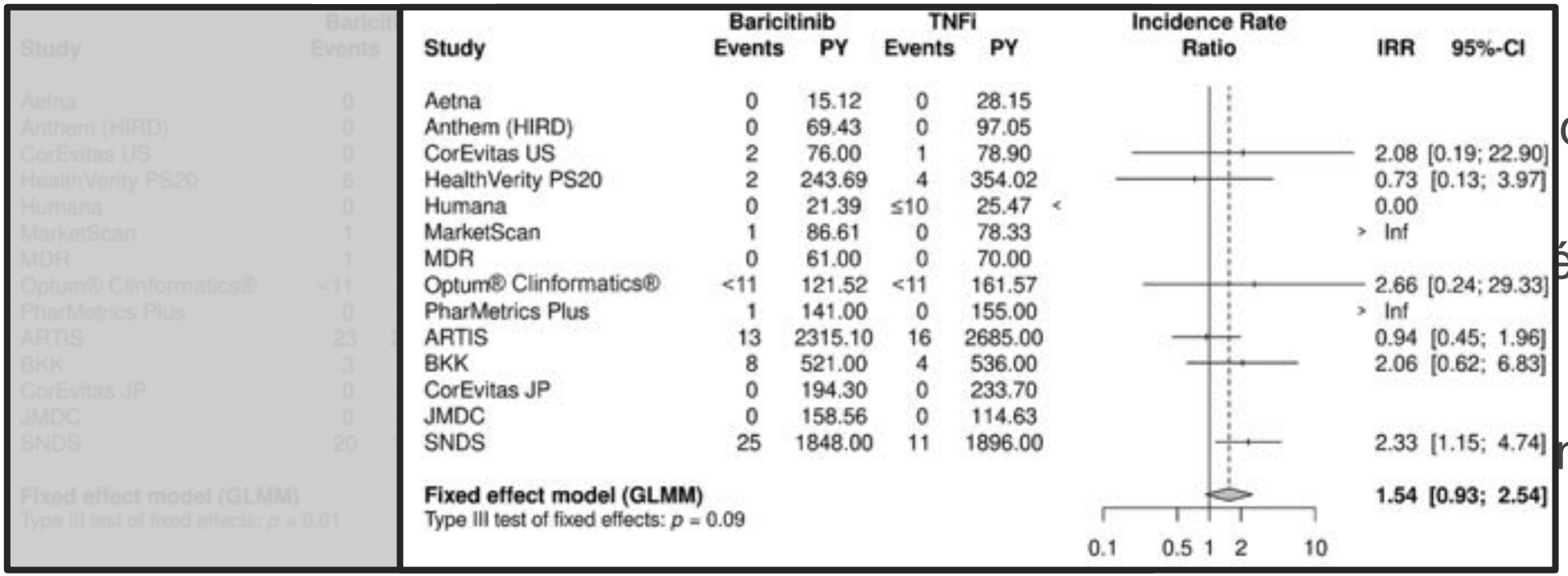
MACE



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Salinas CA, et al. Rheumatol Ther. 2022 Nov 13:1–23

Rheumatol Ther
https://doi.org/10.1007/s40744-022-00505-1

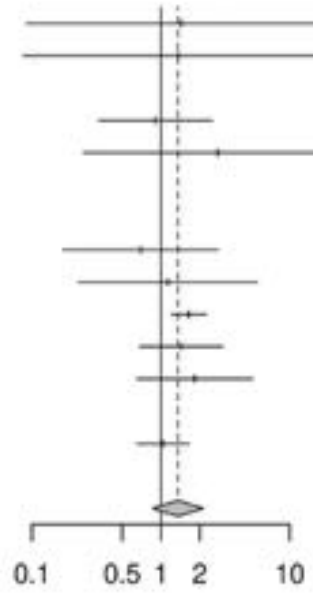
ORIGINAL RESEARCH

Evaluation of VTE, MACE, and Serious Infections Among Patients with RA Treated with Baricitinib Compared to TNFi: A Multi-Database Study of Patients in Routine Care Using Disease Registries and Claims Databases

Serious infections

Study	Baricitinib Events	Baricitinib PY	TNFi Events	TNFi PY	IRR	95%-CI
Aetna	1	16.71	1	23.99	1.44	[0.09; 22.95]
Anthem (HIRD)	≤10	73.30	≤10	100.10	1.37	[0.09; 21.83]
CorEvitas US	3	74.90	0	81.70	> Inf	
HealthVerity PS20	6	240.64	10	362.97	0.91	[0.33; 2.49]
Humana	≤10	19.77	≤10	27.30	2.76	[0.25; 30.46]
MarketScan	1	87.23	0	83.53	> Inf	
MDR	0	60.00	2	66.20	< 0.00	
Optum® Clinformatics®	<11	125.28	<11	174.34	0.70	[0.17; 2.78]
PharMetrics Plus	3	141.90	3	160.80	1.13	[0.23; 5.61]
ARTIS	94	2234.30	66	2589.10	1.65	[1.20; 2.26]
BKK	17	596.40	12	607.80	1.44	[0.69; 3.02]
CorEvitas JP	9	190.80	6	232.90	1.83	[0.65; 5.14]
JMDC	0	155.66	1	128.13	< 0.00	
SNDS	36	1920.00	36	1994.00	1.04	[0.65; 1.65]
Fixed effect model (GLMM)					**1.36**	**[0.86; 2.13]**

Type III test of fixed effects: $p = 0.18$



Salinas CA, et al. Rheumatol Ther. 2022 Nov 13:1–23

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 24 - 27 October 2022

News 28/10/2022

EMA recommends measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

EMA's safety committee (PRAC) has recommended measures to minimise the risk of serious side effects associated with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

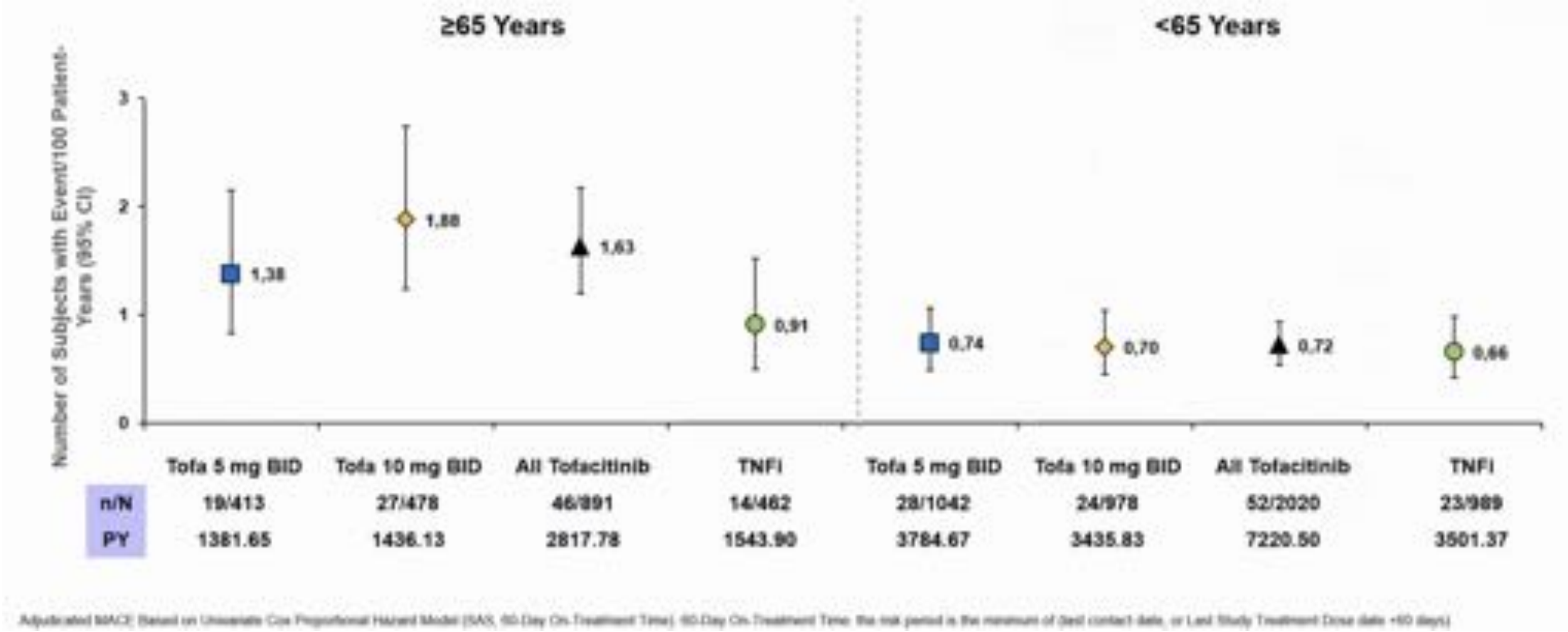
The Committee recommended that these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

The Committee also recommended using JAK inhibitors with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in some patient groups who may be at risk of VTE, cancer or major cardiovascular problems.

Risque cardio-vasculaire

- Quels sont les patients à risque ?
- Quels sont les nouvelles données hors ORAL surveillance ?

Patients les plus à risque dans ORAL surveillance (1)

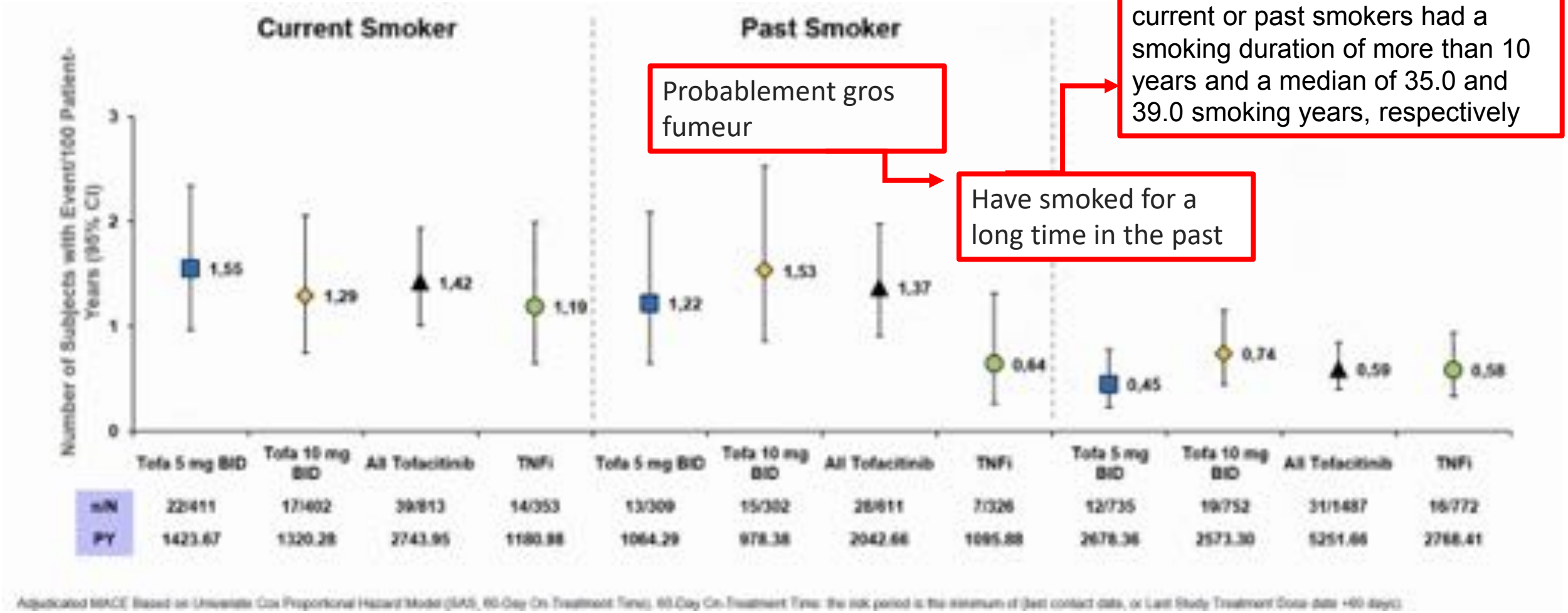


	Tofa 5 mg BID	Tofa 10 mg BID	All Tofacitinib	TNFi	Tofa 5 mg BID	Tofa 10 mg BID	All Tofacitinib	TNFi
n/N	19/413	27/478	46/891	14/462	28/1042	24/978	52/2020	23/989
PY	1381.65	1436.13	2817.78	1543.90	3784.67	3435.83	7220.50	3501.37

Adjudicated MACE: Based on Univariate Cox Proportional Hazard Model (SAS, 60-Day On-Treatment Time). 60-Day On-Treatment Time: the risk period is the minimum of (last contact date, or Last Study Treatment Dose date +60 days)

Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

Patients les plus à risque dans ORAL surveillance (2)



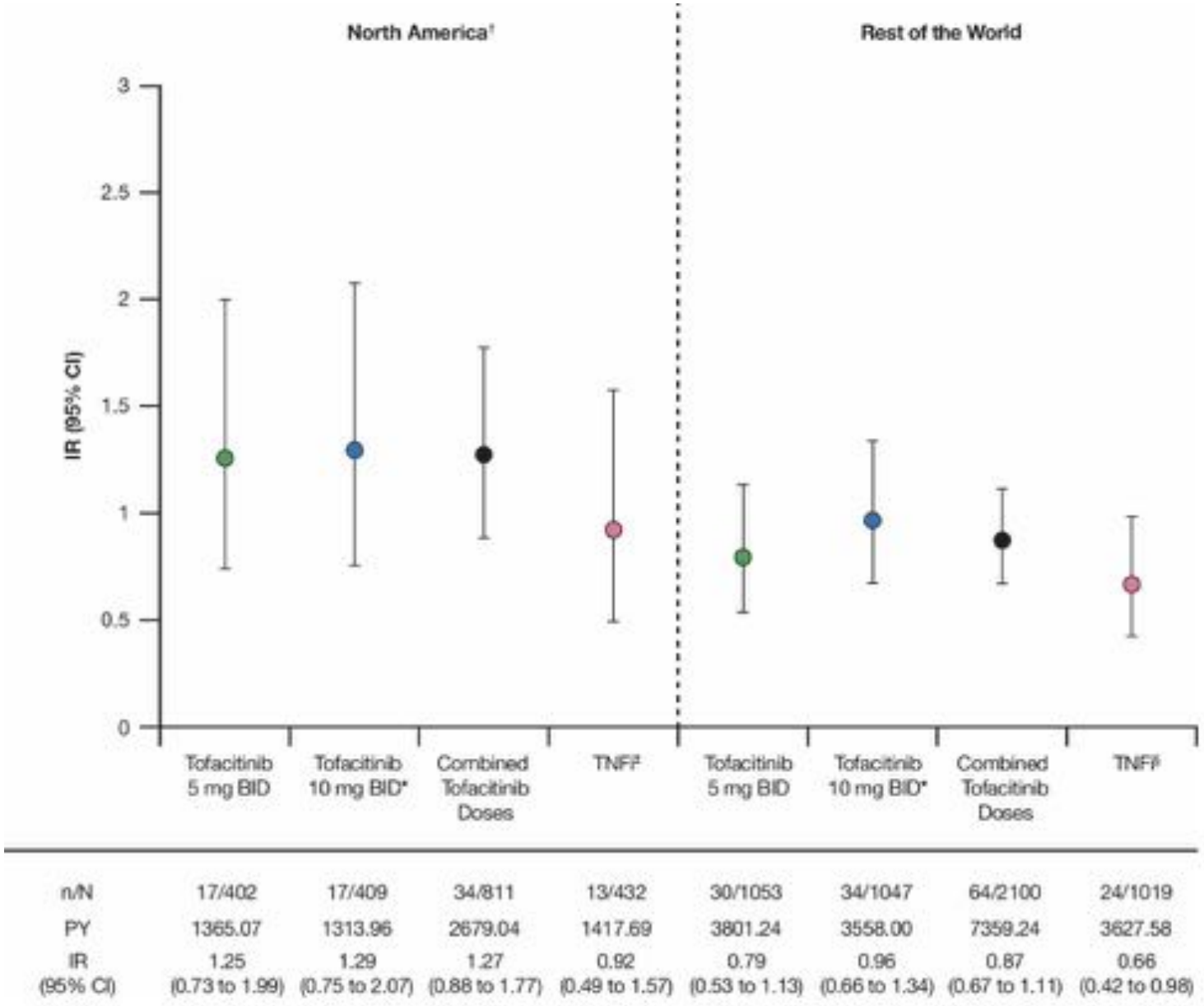
Probablement gros fumeur

Have smoked for a long time in the past

The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively

Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

Patients les plus à risque dans ORAL surveillance (3)



n/N	17/402	17/409	34/811	13/432	30/1053	34/1047	64/2100	24/1019
PY	1365.07	1313.96	2679.04	1417.69	3801.24	3558.00	7359.24	3627.58
IR (95% CI)	1.25 (0.73 to 1.99)	1.29 (0.75 to 2.07)	1.27 (0.88 to 1.77)	0.92 (0.49 to 1.57)	0.79 (0.53 to 1.13)	0.96 (0.66 to 1.34)	0.87 (0.67 to 1.11)	0.66 (0.42 to 0.98)

Comorbidités ↓	Amérique du Nord	ROW
Age ≥ 65 ans, %	40,1%	27,4%
BMI ≥ 30 kg/m^2, %	56,8%	35,6%
HTA, %	71,3%	63,9%
Diabète, %	25%	14,4%
Coronaropathie, %	16,3%	9,4%
IDM, %	6,3%	2,9%
Angor, %	1,1%	0,8%

Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

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CLINICAL SCIENCE

Risk of major adverse cardiovascular events with tofacitinib versus tumour necrosis factor inhibitors in patients with rheumatoid arthritis with or without a history of atherosclerotic cardiovascular disease: a post hoc analysis from ORAL Surveillance

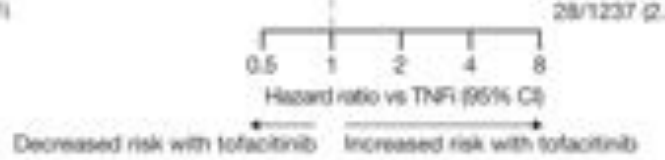
Christina Charles-Schoeman [1], Maya H Buch [2,3], Maxime Dougados [4,5], Deepak L Bhatt [6], Jon T Giles [7], Steven R Ytterberg [8], Gary G Koch [9], Ivana Vranic [10], Joseph Wu [11], Cunshan Wang [11], Kenneth Kwok [12], Sujatha Menon [11], Jose L Rivas [13], Arne Yndestad [14], Carol A Connell [11], Zoltan Szekanecz [15]

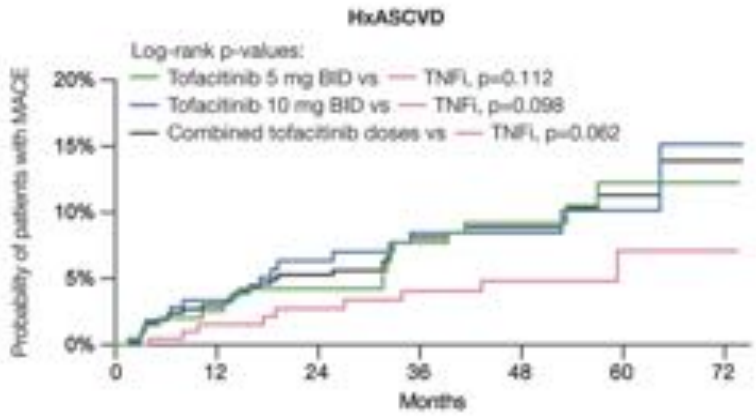
- ASCVD = atherosclerotic cardiovascular disease = ATCD de coronaropathie, d'AVC ou d'artériopathie périphérique
- Les HR ont été évaluées pour l'ensemble de la population et en fonction des antécédents d'ASCVD (analyse exploratoire)

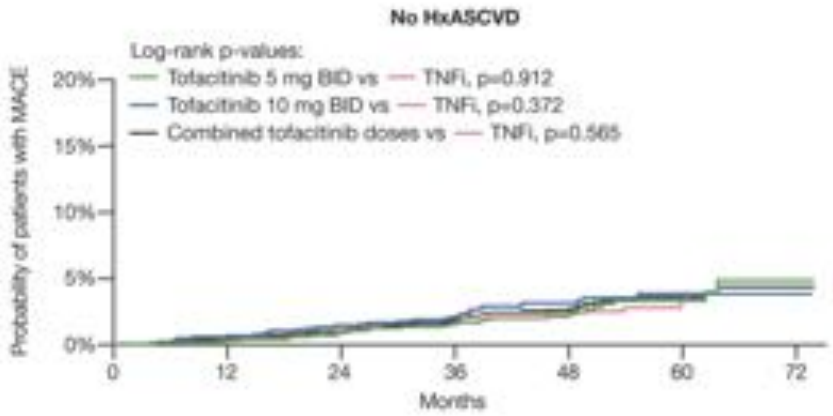
Charles-Schoeman C, et al. ARD 2022

Risque de MACE avec les JAKi vs TNFi en fonction d'un ATCD de maladie cardio-vasculaire

			n/N (%)	HR vs TNFi (95% CI)	IR per 100 PY (95% CI) [PY]	IRD vs TNFi per 100 PY (95% CI)	NNH (PY) vs TNFi[2]	NNH (5-yr) vs TNFi[2]
MACE	Overall population[1] N=4362	Tofacitinib 5 mg BID	47/1455 (3.2%)	1.24 (0.81, 1.91)	0.91 (0.67, 1.21) [5166.3]	0.18 (-0.18, 0.53)	567	113
		Tofacitinib 10 mg BID	51/1456 (3.5%)	1.43 (0.94, 2.18)	1.05 (0.78, 1.38) [4872.0]	0.31 (-0.06, 0.69)	319	64
		Combined tofacitinib doses	98/2911 (3.4%)	1.33 (0.91, 1.94)	0.98 (0.79, 1.19) [10038.3]	0.24 (-0.06, 0.55)	412	82
		TNFi	37/1451 (2.5%)		0.73 (0.52, 1.01) [5045.3]			
	HxASCVD N=640 (14.7%)	Tofacitinib 5 mg BID	17/204 (8.3%)	1.96 (0.67, 4.40)	2.53 (1.47, 4.05) [672.7]	1.24 (-0.22, 2.71)	80	16
		Tofacitinib 10 mg BID	17/222 (7.7%)	2.01 (0.89, 4.50)	2.61 (1.52, 4.18) [651.7]	1.33 (-0.17, 2.82)	75	15
		Combined tofacitinib doses	34/426 (8.0%)	1.98 (0.95, 4.14)	2.57 (1.78, 3.59) [1324.4]	1.28 (0.08, 2.49)*	78	16
		TNFi	9/214 (4.2%)		1.28 (0.59, 2.44) [701.4]			
	No HxASCVD (CV RFs only) N=3722 (85.3%)	Tofacitinib 5 mg BID	30/1251 (2.4%)	1.03 (0.62, 1.73)	0.67 (0.45, 0.95) [4493.6]	0.02 (-0.31, 0.36)	4344	869
		Tofacitinib 10 mg BID	34/1234 (2.8%)	1.25 (0.76, 2.07)	0.81 (0.56, 1.13) [4220.2]	0.16 (-0.20, 0.52)	621	124
		Combined tofacitinib doses	64/2485 (2.6%)	1.14 (0.73, 1.78)	0.73 (0.57, 0.94) [8713.9]	0.09 (-0.21, 0.39)	1113	223
		TNFi	28/1237 (2.3%)		0.64 (0.43, 0.93) [4343.9]			

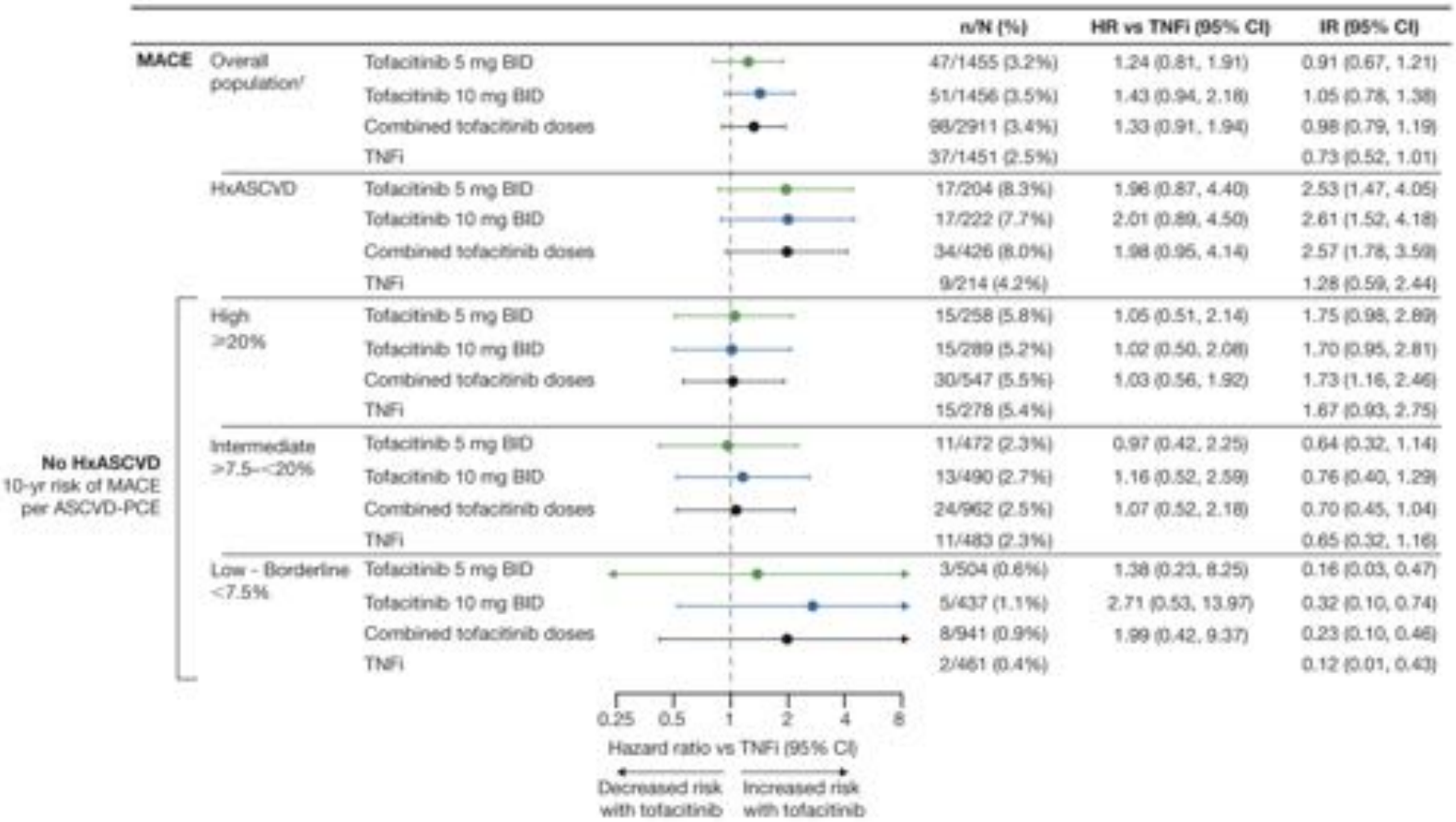






Charles-Schoeman C, et al. ARD 2022

Risque de MACE avec les JAKi vs TNFi, chez les patients sans ATCD de maladie cardio-vasculaire, mais avec FDR CV



Such as heart attack or stroke

Charles-Schoeman C, et al. ARD 2022

Risque cardio-vasculaire

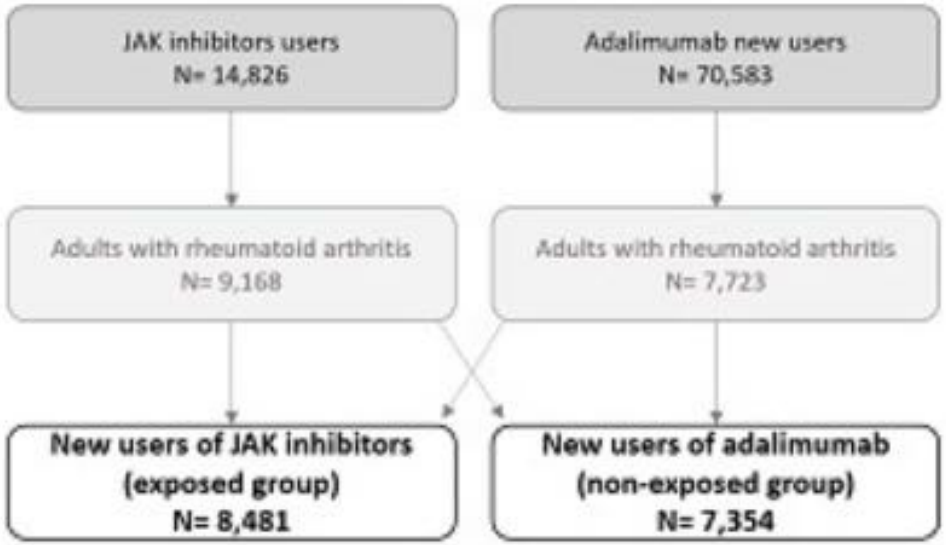
- Quels sont les patients à risque ?
- Quels sont les nouvelles données hors ORAL surveillance ? Quid des autres JAKis ?

EPIDEMIOLOGICAL SCIENCE

Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study

Lea Hoisnard [1,2,3], Laura Pina Vegas [1,3,4], Rosemay Dray-Spira,[5] Alain Weill,[5] Mahmoud Zureik,[5] Emilie Sbidian [1,2,3,5,6]

- Etude sur le SNDS comparant le risque de MACE ou TVP/EP chez les patients débutants un JAKi ou de l'adalimumab pour une PR entre le 1er Juillet 2017 et le 31 Mai 2021



Hoisnard L, et al. ARD 2022 Oct

Caractéristique des populations

	Exposed (JAKi) N=8481	Non-exposed (adalimumab) N=7354
Follow-up duration (days)		
Median (IQR)	440 (203–846)	344 (185–686)
Sociodemographic characteristics		
Age (years), mean (SD)	59.3 (13.3)	55.3 (13.4)
Female sex	6644 (78.3)	5237 (71.2)
Deprivation index	3.0 (1.4)	3.0 (1.5)
Complementary universal health insurance	695 (8.2)	618 (8.4)
Symptomatic agents and DMARDs during 2 years before index date		
csDMARDs		
Methotrexate	2502 (29.5)	3024 (41.1)
Leflunomide	1474 (17.4)	1087 (14.8)
Sulfasalazine	502 (5.9)	492 (6.7)
Hydroxychloroquine	719 (8.5)	578 (7.9)
At least one csDMARD	4279 (50.5)	4233 (57.6)
bDMARDs		
TNF inhibitors (other than adalimumab)	2918 (34.4)	2375 (32.3)
IL-6 inhibitors	2026 (23.9)	392 (5.3)
Abatacept	2002 (23.6)	446 (6.1)
Rituximab	712 (8.4)	74 (1.0)
Anakinra	70 (0.8)	20 (0.3)
Number of bDMARDs		
None	2802 (33.0)	4477 (60.9)
One	3736 (44.1)	2368 (32.2)
Two or more	1943 (22.9)	509 (6.9)
Symptomatic agents		
NSAIDs	3601 (42.5)	3941 (53.6)
Systemic corticosteroids	5711 (67.3)	4361 (59.3)

	Exposed (JAKi) N=8481	Non-exposed (adalimumab) N=7354
Symptomatic agents and DMARDs at index date		
csDMARDs		
Methotrexate	962 (11.3)	1508 (20.5)
Leflunomide	438 (5.2)	396 (5.4)
Sulfasalazine	61 (0.7)	56 (0.8)
Hydroxychloroquine	186 (2.2)	111 (1.5)
At least one csDMARD	1600 (18.9)	2043 (27.8)
Symptomatic agents		
NSAIDs	886 (10.5)	808 (11.0)
Systemic steroids	3489 (41.1)	2353 (32.0)
Comorbidities		
Cardiovascular risk and treatments		
Cardiovascular disease or VTE identified within 10 years	1001 (11.8)	624 (8.5)
Diabetes	914 (10.8)	587 (8.0)
Essential hypertension		(20.2)
Dyslipi		(6.3)
Morbid		7.2)
Tobacco		.1)
COPD		15.0)
Antiplate		655 (8.9)
Anticoagulants	419 (4.9)	267 (3.6)
Other comorbidities		
Atherosclerosis of arteries of extremities	201 (2.4)	122 (1.7)
Chronic renal failure	170 (2.0)	74 (1.0)
Heart failure	245 (2.9)	102 (1.4)
Cancer	362 (4.3)	250 (3.4)

Plus de comorbidités

Hoisnard L, et al. ARD 2022 Oct

Résultats

Table 2 Numbers and incidence rates of major adverse cardiovascular events (MACEs) and venous thromboembolism events (VTEs) by exposure

	MACEs				VTEs			
	Number of events	Incidence per 1000 PY (95% CI)	Number of acute myocardial infarctions	Number of ischaemic strokes	Number of events	Incidence per 1000 PY (95% CI)	Number of pulmonary embolisms	Number of venous embolism and thrombosis
Exposed (JAKi), N=8481	54	4.3 (3.1 to 5.4)	29	28	75	6.0 (4.6 to 7.3)	41	34
Tofacitinib, N=3416	14	2.8 (1.4 to 4.3)	8	6	29	5.9 (3.7 to 8.0)	12	17
Baricitinib, N=5065	40	5.2 (3.6 to 6.8)	21	22	46	6.0 (4.3 to 7.7)	29	17
Non-exposed (adalimumab), N=7354	35	3.6 (2.4 to 4.9)	24	11	32	3.3 (2.2 to 4.5)	14	18

JAKi, Janus kinase inhibitor; PY, person-years.

Table 3 Risk of MACEs and/or VTEs by exposed compared with non-exposed to a JAKi

	MACEs		VTEs	
Analysis	CSHR/SHR (95% CI)	P value	CSHR/SHR (95% CI)	P value
Cox model crude analysis	1.2 (0.8 to 1.9)	0.37	1.9 (1.2 to 2.8)	0.003
Cox model with time-dependent covariate*	1.2 (0.8 to 1.8)	0.43	1.8 (1.2 to 2.7)	0.007
Cox model with stabilised weights and time-dependent covariate—CSHRw†	1.0 (0.7 to 1.5)	0.99	1.1 (0.7 to 1.6)	0.63
Fine-Gray—weighted subhazard ratio‡	1.0 (0.7 to 1.5)	1.0	1.2 (0.8 to 1.7)	0.43
Adjusted Cox model with time-dependent covariate—CSHRa§	0.9 (0.6 to 1.4)	0.66	1.2 (0.8 to 1.8)	0.50

Conclusion

- Données rassurantes sur le risque de MACE ou TVP/EP dans une population Française traitées par JAKi, même chez des patients à haut risque CV

Hoisnard L, et al. ARD 2022 Oct 5

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EPIDEMIOLOGICAL SCIENCE

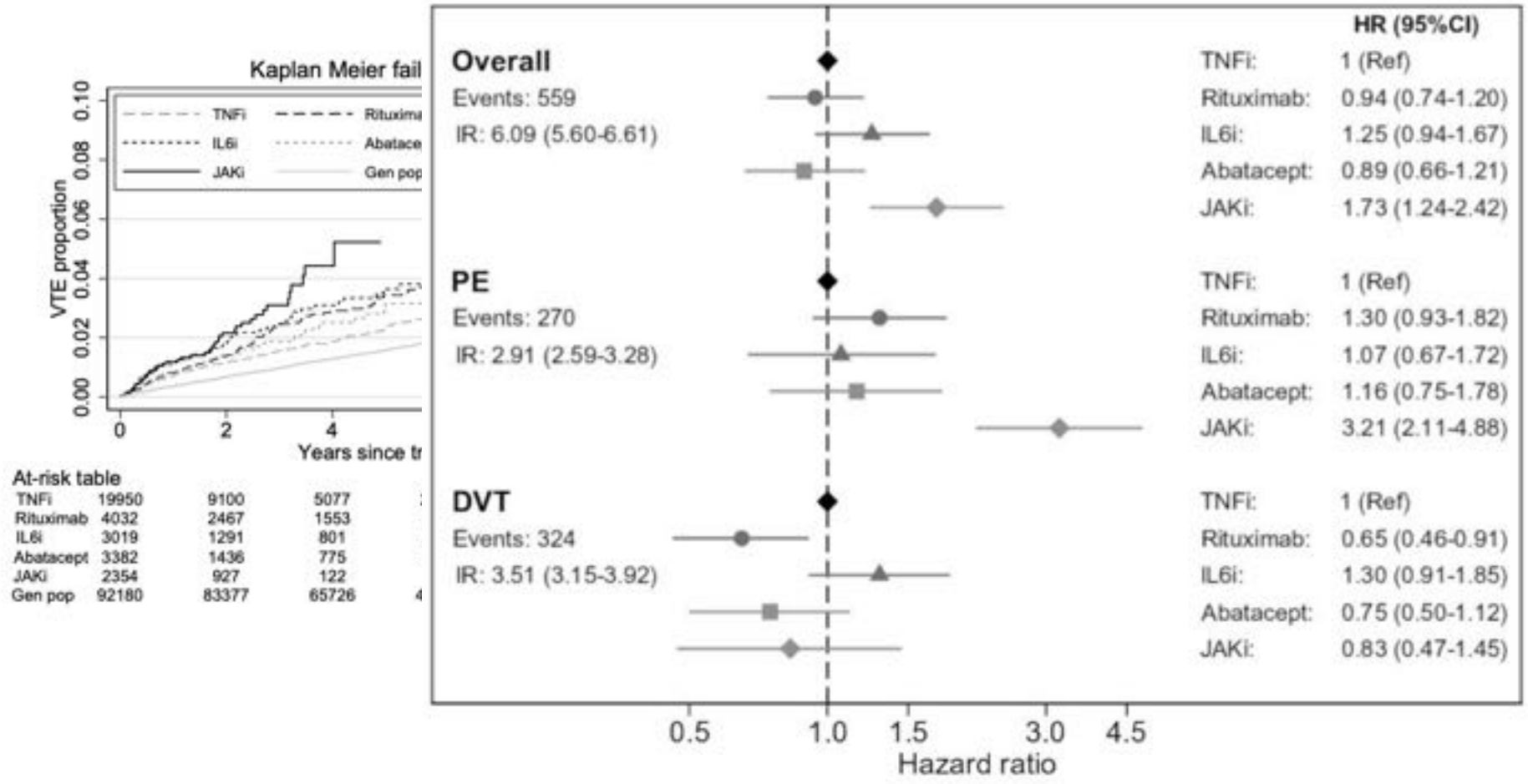
Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis

Viktor Molander ,[1,2] Hannah Bower ,[1] Thomas Frisell ,[1] Benedicte Delcoigne ,[1] Daniela Di Giuseppe,[1] Johan Askling ,[1,2] The ARTIS study group

- Évaluer l'incidence des TVP et EP chez PR traités par JAKi, TNFi ou autres bDMARD (+ données de la pop générale Suédoise)
- Registre ARTIS de 2010 à 2021 (n=32737 initiations de traitement).
- Résultat = temps écoulé jusqu'au 1er évènements

Molander V, et al. ARD 2022 Sep

Résultats



standardised incidence rates, and HRs for VTE in Swedish rom the general population between 2010 and 2020

HR (95% CI) Model 1*	HR (95% CI) Model 2†	HR (95% CI) Model 3‡
1 (ref)	1 (ref)	1 (ref)
1.09 (0.86 to 1.38)	0.97 (0.76 to 1.23)	0.94 (0.74 to 1.20)
1.44 (1.09 to 1.92)	1.30 (0.97 to 1.73)	1.25 (0.94 to 1.67)
1.10 (0.81 to 1.49)	0.89 (0.65 to 1.20)	0.89 (0.66 to 1.21)
1.94 (1.40 to 2.70)	1.63 (1.17 to 2.28)	1.73 (1.24 to 2.42)
2.00 (1.41 to 2.83)	1.69 (1.19 to 2.40)	1.79 (1.25 to 2.55)
1.91 (0.89 to 4.11)	1.56 (0.72 to 3.35)	1.66 (0.77 to 3.59)
n/a	n/a	n/a
0.66 (0.57 to 0.76)	n/a	n/a

Conclusion

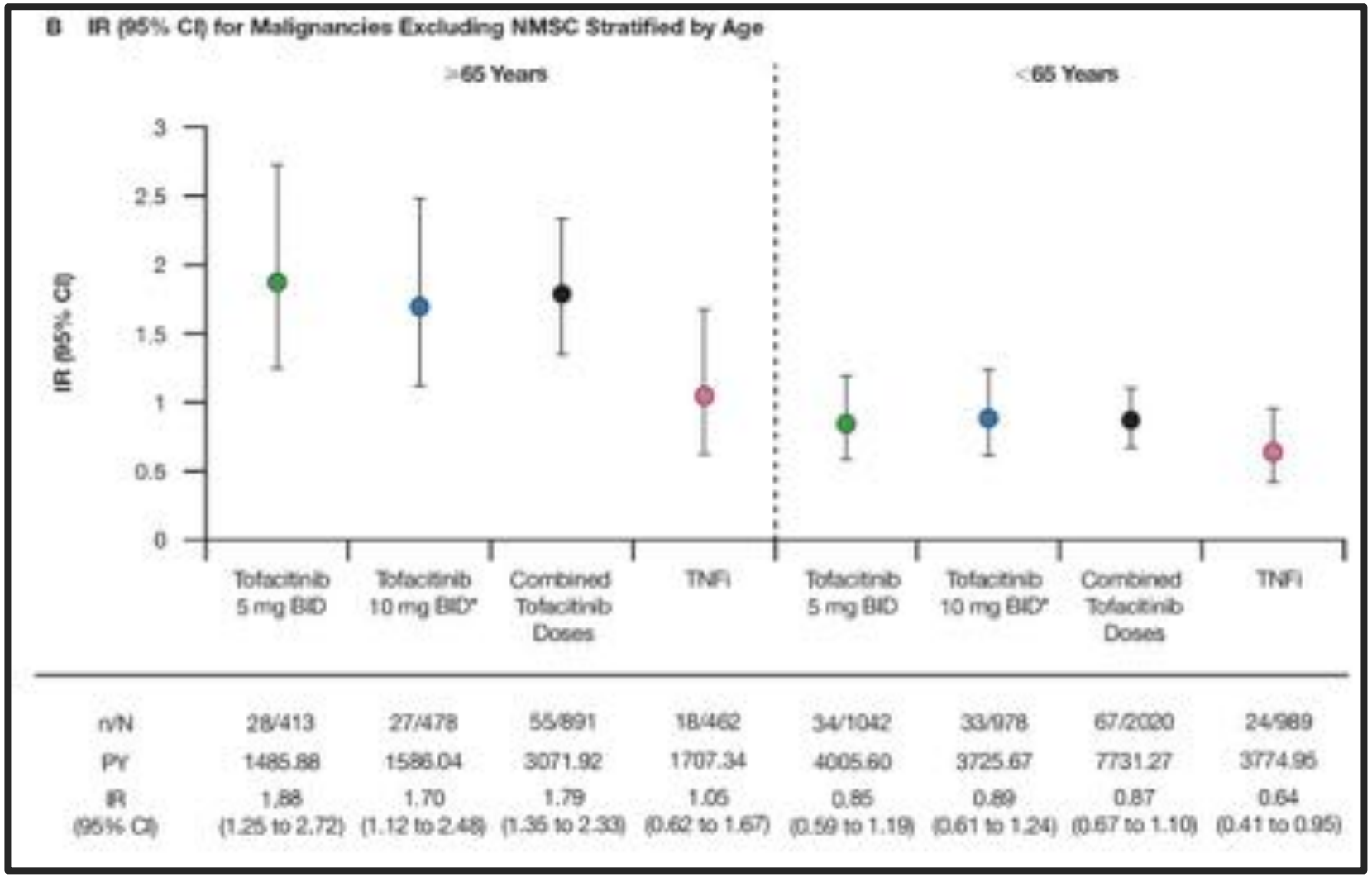
- Augmentation du risque d'embolie pulmonaire sous JAKi dans un population Suédoise

Molander V, et al. ARD 2022 Sep

Risque néoplasique

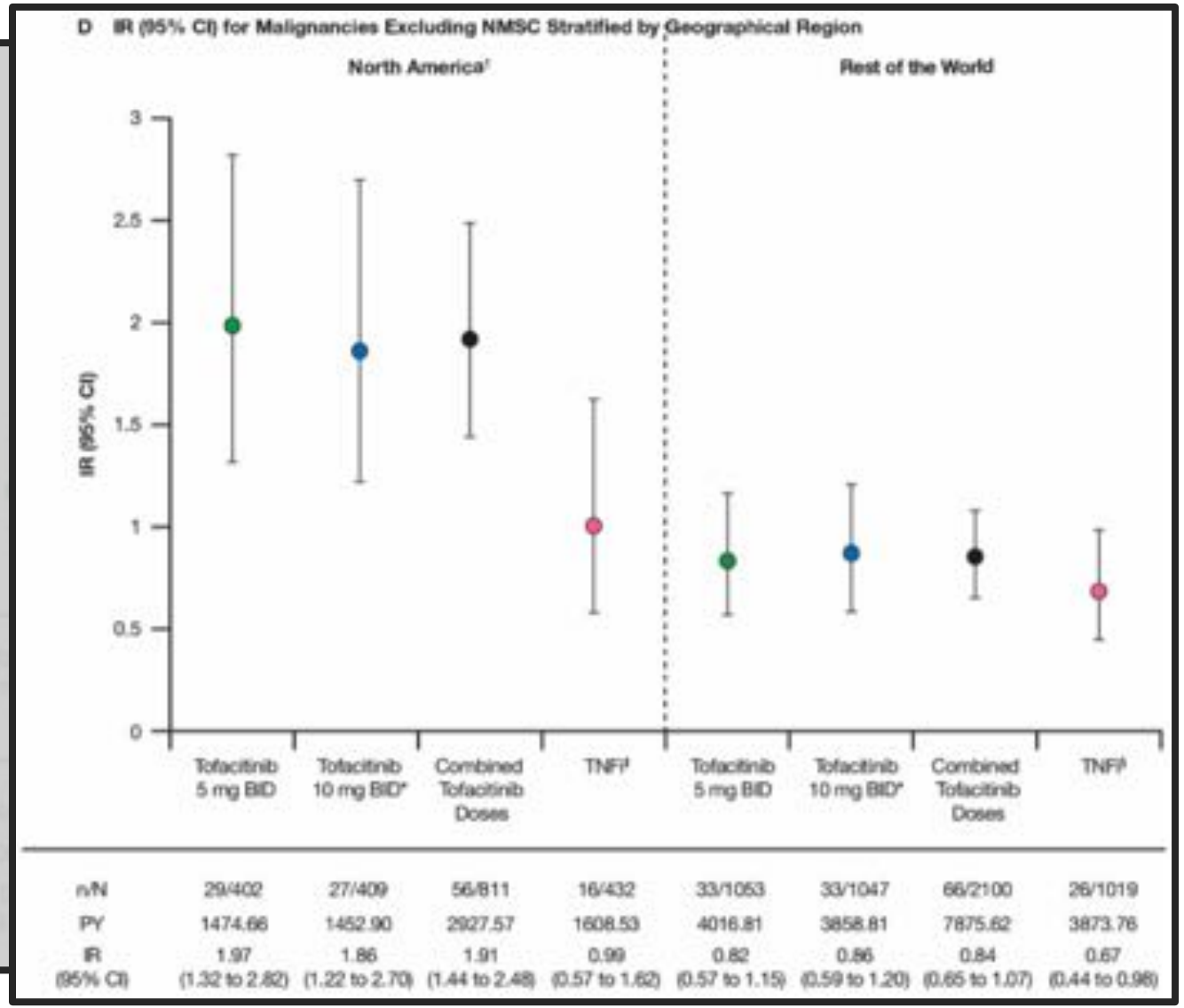
- Quels sont les patients à risque ?
- Quels sont les nouvelles données hors ORAL surveillance ?

ORAL surveillance : risque néoplasique



Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

ORAL surveillance : risque néoplasique



Ytterberg S R, et al. NEJM 2022 Jan 27;386(4):316-326

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ACR Convergence
Where Rheumatology Meets
#ACR22

JAK inhibitors and Risk of Cancer

Analysis of the French national healthcare insurance system cohort

Amandine Gouverneur[1], Jérôme Avouac[2], Clément Prati[3], Jean-Luc Cracowski[4], Thierry Schaeverbeke[5], Antoine Pariente[1], and Marie-Elise Truchetet[5]

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[3] University Hospital - CHU Minjoz, Rheumatology Unit, Besancon, France

[4] Université Grenoble Alpes, INSERM, HP2, Grenoble, 38000, France

[5] Department of Rheumatology, National Reference Center for Systemic Autoimmune Rare Diseases, Hopital Pellegrin, Bordeaux, France

Events and propensity score analyses

Among the overall matched population, 64 (1.0%) patients had a diagnosis of cancer, 25 (0.8%) treated with JAKi and 39 (1.3%) treated with TNFi

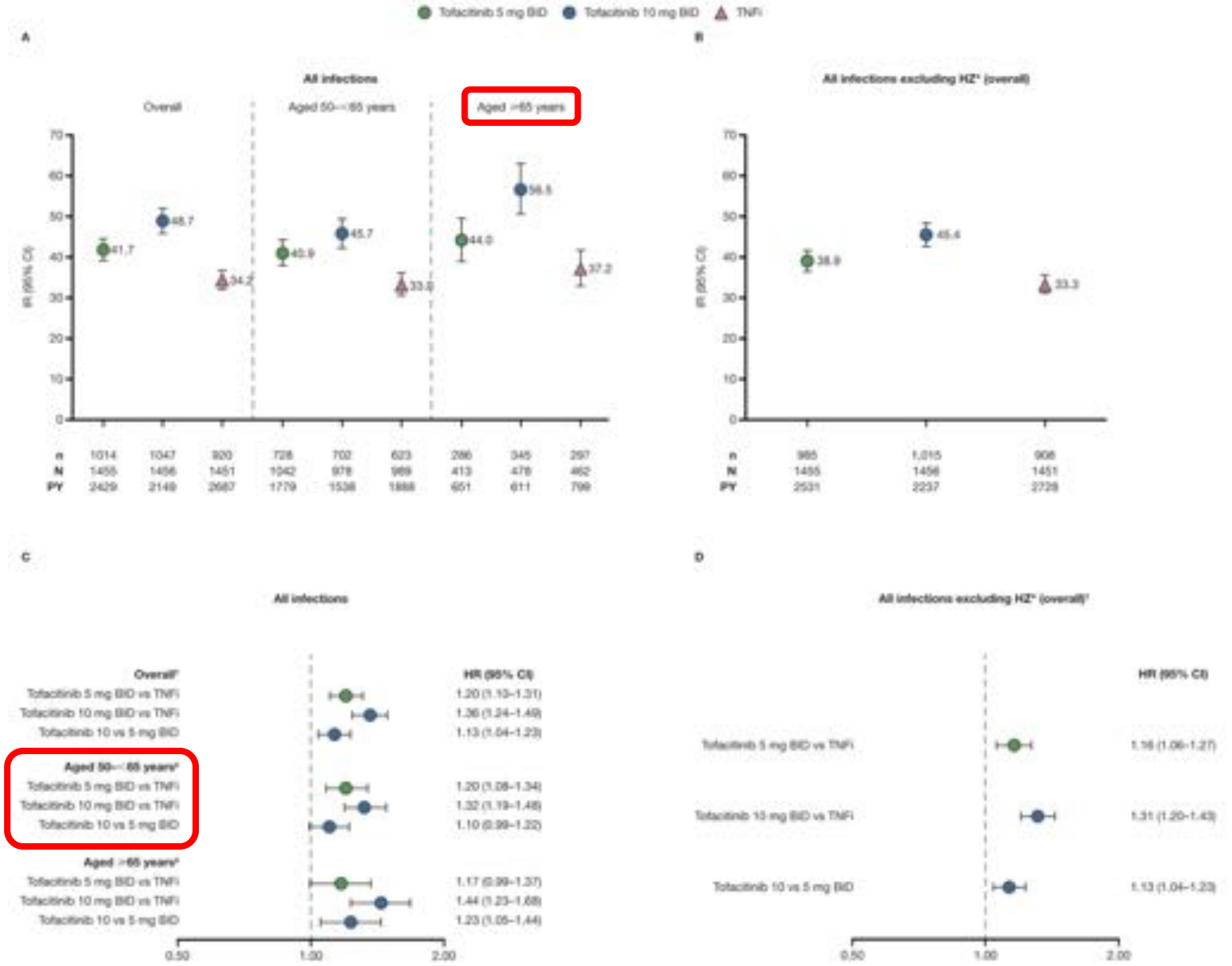
	Hazard ratio, [95%CI]	P
Models before matching		
Crude model	0.90 [0.63-1.30]	0.5821
Adjustment on the inverse probability of treatment weighting (IPTW)	0.73 [0.50-1.07]	0.1093
Model after matching		
Crude model	**0.71 [0.43-1.18]**	**0.1843**

Sensitivity analysis (All cancer events at least 3 months after the index date): similar results

Risque infectieux

- Quels sont les patients à risque ?
- Quels sont les nouvelles données hors ORAL surveillance ? Quid des autres JAKis ?

ORAL surveillance : risque infectieux



Balanescu A-R, et al. ARD 2022;81:1491–1503

Et maintenant ?

- Le PRAC
- Les recommandations des sociétés savantes
- Et nos capacités d’adaptation

Quelles sont les prochaines étapes pour y voir plus clair ?

Données chez des patients en échec du MTX. Quid en post bDMARD ?

- De nouvelles indications avec des comorbidités différentes et des doses de JAKi différentes
- Des données plus détaillées d'ORAL Surveillance. Plus de description des cancers !
- Des données importantes avec le baricitinib
  - RA-BRIDGE ; 4V-MC-JAJA
- Et toujours plus de données de LTE et de vraies vies

TATA : un registre en France !

Registre national de la Société Française de Rhumatologie des patients traités par inhibiteurs de JAK